specification together with the knowledge of one skilled in the art would not lead to a conclusion that undue experimentation would be required to practice the claimed subject matter.

The claims recite, in part, naturally occurring variants of OPG.

Claims 37 and 49 (and claims depending therefrom) are directed to antibody compositions which specifically bind OPG binding proteins, including naturally occurring variants of OPGbp. The specification discloses naturally occurring variants of OPGbp at p. 15, lines 9-12 as follows:

> Fragments or analogs may be naturally occurring, such as a polypeptide product of an allelic variant or a mRNA splice variant, ...

Naturally occurring variants of OPGbp represent a subset of OPGbp variants which are alternative forms of OPGbp that exist in nature.

The specification contains sufficient guidance for one skilled in the art to carry out the invention without undue experimentation.

The specification teaches the nucleotide and amino acid sequences of murine and human OPGbp. The specification also teaches hybridization using a murine OPGbp probe to isolate a human OPGbp nucleotide sequence. It would be well within the ability of one skilled in the art to isolate naturally occurring variants of human or murine OPGbp using the disclosed hybridization techniques, or variations thereof. As pointed out previously, techniques for generating OPGbp antibodies and measuring binding of OPGbp antibodies to OPGbp are also disclosed in the application, and such techniques may be readily applied to antibodies which bind naturally occurring variants of OPGbp.

No evidence has been presented that naturally occurring OPGbp variants could not be immunogenic.

The Examiner argues for unpredictability in the art citing Bork (Genome Research 10, 398-400 (2000); Skolnick et al. (Trends in Biotech. 18, 34-39 (2000)); and Deorks et al. (Trends in Genetics 14, 248-250 (1998)). The references are alleged to show that protein function cannot be predicted from structure and that amino acid substitutions may very likely disrupt protein structure and/or function, including immunogenicity. However, the Bork, Skolnick and Deorks references only discuss the possible effects of introducing artificial mutations into proteins (by site-directed mutagenesis, for example) and do not discuss naturally occurring variants at all. The references cited by the Examiner are simply not relevant to the claimed subject matter and provide no evidence whatsoever that naturally occurring OPGbp variants could not be used as immunogens for the production of antibodies.

The Sullivan Declaration demonstrates that the disclosure enables the claimed invention.

In response to the rejection for lack of enablement under section 112, Applicant submitted a Declaration of John K. Sullivan which described the generation of anti-OPGbp antibodies which inhibit bone resorption. The declaration stated that, using the procedures described in the application, one skilled in the art was able to generate anti-OPGbp antibodies useful for treating bone diseases.

The Examiner agreed that the declaration provides evidence that the specification is enabling for OPGbp antibodies which inhibit bone resorption, albeit only when the antibodies are raised to certain immunogens. In particular, it is argued that the declaration did not disclose antibodies made to OPGbp variants, and therefore Applicant is not entitled to OPGbp antibodies which bind variants.

Applicant submits that the Examiner misses the point of the declaration. The declaration showed an example of anti-OPGbp antibodies which inhibit bone resorption prepared by the methods described in the specification. It is apparent that the method could be applied to various other OPGbp immunogens, including naturally occurring variants of OPGbp. There is no requirement that Applicant provide evidence for each and every immunogen of OPGbp provided a working method for making the claimed antibodies is disclosed. The declaration clearly shows this. Moreover, the Examiner has not cited any evidence whatsoever to suggest that the methods disclosed in the application could not be used with a wide range of OPGbp immunogens.

In view of the above remarks, Applicant requests withdrawal of the rejection.

Claims 37-57 are rejected under 35 U.S.C. 112, first paragraph, as the subject matter of the claims is allegedly not described in the specification. The Examiner argues that a naturally occurring variant of OPGbp and antibody composition which binds to an epitope of a naturally occurring variant of OPGbp is not described. Applicants disagree.

As stated in 35 U.S.C. 112, first paragraph, "[t]he specification shall contain a written description of the invention ... " (Emphasis added). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending upon the nature of the invention claimed." *Vas-Cath, Inc. v. Mahurkar* 19 USPQ2d at 1116 (Fed. Cir. 1991). Thus, a rejection based upon lack of written description must properly identify "the invention".

The invention relates to antibody compositions which specifically bind to the recited OPGbp molecules, and therefore the written description requirement must, in the first instance, be applied to the antibody compositions. On p. 17, line 17 of the specification, the specification discloses antibodies which specifically bind OPGbp polypeptides of the invention and may be used to treat bone diseases. Example 11 starting on p. 46 of the specification discloses methods by which antibodies may be prepared against various polypeptides and peptides of the invention. The specification specifically discloses OPGbp polypeptides comprising SEQ ID NO:37 and SEQ ID

NO:39 and contemplates other polypeptides against which antibodies may be prepared. Moreover, the structure of antibodies was known in the art, as stated in the "Synopsis of Application of Written Description Guidelines at p. 59:

> The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding site in the form of complementarity determining regions as well as the variable regions subgroups (framework regions) from a variety of species are known and published in the art. It is also well known that antibodies can be made against virtually any protein.

Given the knowledge of antibody structure available to one skilled in the art together with the disclosure of OPGbp antibodies in the specification, it is clear that the claimed antibody compositions satisfy the written description requirements.

The Examiner has argued in the Office Action dated March 12, 2001 that only those claimed antibody compositions directed against sequences disclosed in SEQ ID NO:37 or SEQ ID NO:39 are described, citing *Fiers v. Sugano* 25 USPQ2d 1601 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co.* 18 USPQ2d 1016 (Fed. Cir. 1991). The cases cited by the Examiner state in part that claims directed to nucleotide and/or amino acid sequences require disclosure of at least some structure or sequence which can distinguish the claimed sequences from others. The Examiner has also cited *Fiddes v. Baird* 30 USPQ2d 1481 (Fed. Cir. 1993) in which claims to mammalian fibroblast growth factor (FGF) were unpatentable for lack of written description where the sequence of only bovine FGF was disclosed in the specification.

Applicant maintains that the Examiner has not established a lack of written description in the present case. The Examiner's arguments and the cited case law have focused solely on OPGbp molecules to which the antibodies bind, and not on the invention which is the antibody compositions. The Examiner has not provided any evidence why the antibody compositions are not adequately described. The argument that OPGbp antibodies are only described if the sequences of OPGbp molecules to which they bind are disclosed is simply an improper determination of written description and is in total contradiction to the numerous patents currently in force which claim antibodies that bind to polypeptides where no polypeptide sequence has been disclosed. Indeed, in the Patent Office's own guidelines, a claim to an antibody which is capable of binding antigen X is considered to meet the written description requirements in the absence of any sequence information regarding antigen X.

In view of the above remarks, it is requested that the rejection be withdrawn.

CONCLUSION

Claims 37-57 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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